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Noninvasive Assessment of Acute Effects of Nifedipine on Rest and Exercise Hemodynamics and Cardiac Function in Patients With Aortic Regurgitation

WEI FENG SHEN, MSc (MED), GARY S. ROUBIN, MB, FRACP, KUNIHIKO HIRASAWA, MD, ROGER F. UREN, MB, BRIAN F. HUTTON, MSc, PHILLIP J. HARRIS, MB, DPHIL, FRACP, FACC, PETER J. FLETCHER, MB, PHD, FRACP, DAVID T. KELLY, MB, FRACP, FACC

Sydney, Australia

The acute effects of nifedipine (20 mg sublingually) on hemodynamics and cardiac function were studied at rest and during supine bicycle exercise in 20 patients with aortic regurgitation. At rest, heart rate increased by 13%, systemic vascular resistance decreased by 34% and regurgitant index decreased by 17%. The change in systemic vascular resistance was related to its initial rest level ($r = 0.82$, $p < 0.001$) and to the changes in forward cardiac output ($r = 0.58$, $p < 0.01$) and regurgitant index ($r = 0.60$, $p < 0.01$). Left ventricular end-diastolic and end-systolic volumes, stroke volume and ejection fraction were unchanged, whereas right ventricular ejection fraction increased.

During exercise, nifedipine administration further increased heart rate by 8% and decreased systemic vascular resistance by 19%. Both forward stroke volume and forward cardiac output increased, but total left ventricular stroke volume was unchanged, resulting in a significant decrease in regurgitant index. Although left ventricular end-diastolic volume was slightly decreased, end-systolic volume did not increase; thus, ejection fraction was higher than that during control exercise ($p < 0.01$). Right ventricular ejection fraction increased further.

In aortic regurgitation, the acute administration of nifedipine improved cardiac performance and reduced regurgitation at rest and during exercise as a result of afterload reduction and increased heart rate. Whether these beneficial effects will occur during long-term therapy requires further investigation.

Vasodilators may improve left ventricular function and clinical functional class by reducing afterload in patients with myocardial dysfunction (1–7). In patients with aortic regurgitation, vasodilators have been shown to improve left ventricular function and exercise capacity because they lower arterial resistance (6–8).

Nifedipine is a potent arteriolar vasodilator. Its effects on hemodynamics at rest in patients with aortic regurgitation have recently been reported (8,9), but the effects during exercise have not been well documented. The purpose of this study was to investigate the acute effects of nifedipine administration on both rest and exercise hemodynamics and cardiac function in patients with chronic aortic regurgitation.

From Hallstrom Institute of Cardiology, University of Sydney and Department of Nuclear Medicine, Royal Prince Alfred Hospital, Sydney, Australia. Manuscript received March 7, 1984; revised manuscript received May 30, 1984, accepted June 12, 1984.

Address for reprints: Professor David T. Kelly, Hallstrom Institute of Cardiology, Royal Prince Alfred Hospital, Camperdown, New South Wales 2050, Australia.

Methods

Study patients. Twenty patients (15 men and 5 women, mean age 44 years) with at least moderately severe aortic regurgitation, defined as pulse pressure greater than 55 mm Hg, cardiomegaly on chest radiography and increased left ventricular end-diastolic dimension on echocardiography, were studied. Sixteen patients had cardiac catheterization and greater than 2^+ aortic regurgitation. Aortic regurgitation was caused by rheumatic fever in 14 patients, congenital abnormalities in 4 and cystic medionecrosis in 2. Three patients were taking digitalis, 2 were taking diuretic drugs, 1 was taking a beta-adrenergic blocking agent and the remaining 14 had no medications. All patients had normal sinus rhythm. Patients with acute aortic regurgitation, associated mitral valve disease, aortic stenosis or cardiomyopathy were excluded on the basis of clinical history, physical examination and two-dimensional echocardiography.

In 14 patients without valvular regurgitation who had undergone cardiac catheterization for assessment of coronary artery disease, the radionuclide regurgitant index was

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measured at rest and during exercise before and after nifedipine administration. Approval for the study was given by the Institutional Ethics Committee.

Radionuclide determination of cardiac function. Cardiac blood pool imaging was performed with the patient in the supine position under a single crystal gamma camera (Technicare Ohio, Sigma 420) fitted with a 30° slant hole, high sensitivity collimator and interfaced to a digital computer (PDP 11/34). After in vivo labeling of red blood cells with 20 to 25 mCi of technetium-99m using a standard method (10–13), the camera was positioned in the 30 to 45° left anterior oblique projection. The caudal tilt of the camera was adjusted carefully to clearly separate the atria from the ventricles. Data were recorded in a 64 × 64 matrix, and the average cardiac cycle was divided into 24 frames.

Radionuclide data analysis was performed by a semiautomatic edge detection program (11). We previously described (12) the method for defining left ventricular region of interest at end-diastole and end-systole. In our laboratory, left ventricular ejection fraction measured by the radionuclide method correlated well with that derived from contrast angiographic technique (11,12), and the nongeometric radionuclide estimation of left ventricular volumes has been validated (13) where the absolute left ventricular end-diastolic volume = 2.94 × attenuated radionuclide left ventricular end-diastolic volume + 2.3 ml ($r = 0.98$, SEE = 14 ml).

The right ventricular end-diastolic region was defined on a simultaneously displayed original end-diastolic image and stroke volume image and delineated by using a double cursor technique. This region was used by the computer program to search for a valid right ventricular end-diastolic edge. The right ventricular end-systolic region was selected on an end-systolic image displayed beside an end-systolic binary edgemap. Using both images, the right ventricular end-systolic region was drawn manually and used by the computer program to search for a valid end-systolic region of interest. The number of counts within end-diastolic and end-systolic regions of interest was then determined. Right ventricular ejection fraction was calculated by a standard method (14). To determine the accuracy of this gated equilibrium method of measuring right ventricular ejection fraction, we performed first pass imaging in 19 patients before gated equilibrium studies. The right ventricular ejection fraction correlated well between the two methods ($r = 0.95$, $p < 0.001$). Right ventricular stroke volume was determined by a count-based technique (14). In our laboratory, the radionuclide stroke volume correlated well with the thermodilution stroke volume: thermodilution stroke volume = 2.61 × radionuclide right ventricular stroke volume + 14 ml ($r = 0.87$, SEE = 8.6 ml), and the changes in stroke volumes measured by these two techniques were parallel in direction and magnitude during graded exercise (unpublished observations).

The regurgitant index was calculated as the ratio between left and right ventricular stroke counts (15,16). The relation between radionuclide regurgitant index at rest and angiographic regurgitant fraction in 15 patients who had cardiac catheterization within 1 week of radionuclide studies was expressed as: radionuclide regurgitant index = 0.062 × angiographic regurgitant fraction − 0.454 ($r = 0.93$, $p < 0.001$).

Study protocol. Patients performed supine bicycle exercise on an exercise table (Atomic Products) with the electronically braked ergometer (Siemens-Elema) set at table height. The initial work load of 15 W was increased progressively every 3 minutes by 15 or 30 W depending on the patient's exercise tolerance. Exercise was limited by fatigue or dyspnea, or both, in all patients with aortic regurgitation and by angina in all patients without valvular regurgitation. Radionuclide counts were collected for 6 minutes at rest and during the last 2 minutes of each exercise level. A peripheral venous blood sample was drawn immediately after each imaging for determining blood count rate. Blood pressure was measured with a standard sphygmomanometer cuff by a single observer. Duplicate readings were made at rest and at each level of exercise. Phase IV Korotkov sound (muffling) was recorded as diastolic pressure. A CM_5 electrocardiographic lead was monitored continuously and a 12 lead electrocardiogram was recorded at rest and every minute during exercise on an Avionics Exerstress 4000 system.

After control exercise, patients rested for 2 hours. Nifedipine, 20 mg, was given sublingually. Twenty minutes later, heart rate, blood pressure and gated blood pool imaging were repeated at rest and during exercise at work loads identical to those of the control study.

The following calculations were performed: Rate-pressure product = systolic blood pressure × heart rate. Mean arterial pressure = D + (S − D)/3, where S = the systolic blood pressure and D = the diastolic blood pressure. Systemic vascular resistance ($dynes \cdot s \cdot cm^{-5}$) = (MAP/CO) × 80, where MAP = mean arterial pressure and CO = forward cardiac output. Forward cardiac output = right ventricular stroke volume × heart rate; total cardiac output = left ventricular stroke volume × heart rate. Pressure-volume ratio = systolic blood pressure/left ventricular end-systolic volume; this was used as an indirect measure of myocardial contractility (17,18).

Statistical analysis. Data were analyzed by two-way analysis of variance. When there was a significant difference between the four treatments (rest and exercise before and after nifedipine administration), the treatment means were compared using a modified *t* statistic incorporating the pooled error mean square, with significance levels for four planned comparisons derived from the Bonferroni two-tailed *t* table (19). The relation between variables was tested using linear regression analysis. Data are expressed as mean ± 1 standard deviation.

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Table 1. Effects of Nifedipine on Hemodynamics and Cardiac Function in 20 Patients With Aortic Regurgitation

Variable	Rest		Exercise	
	Before N	After N	Before N	After N
HR (beats/min)	68 ± 10	77 ± 9*	117 ± 13‡	125 ± 16*‡
MAP (mm Hg)	83 ± 7	75 ± 7*	108 ± 12‡	99 ± 13*‡
RPP (× 100)	95 ± 22	94 ± 18	222 ± 44‡	233 ± 64‡
RVSV (ml)	59 ± 13	71 ± 15*	74 ± 20‡	83 ± 19*‡
RVCO (liters/min)	4.1 ± 0.6	5.6 ± 1.1*	8.8 ± 2.2‡	10.8 ± 2.6*‡
LVSV (ml)	139 ± 38	139 ± 36	131 ± 38	134 ± 31
LVCO (liters/min)	9.6 ± 3.3	10.9 ± 3.1	15.4 ± 4.0‡	17.4 ± 4.1*‡
SVR (dynes·s·cm^{-5})	1695 ± 298	1114 ± 168*	1030 ± 226‡	761 ± 201*‡
LVEDV (ml)	242 ± 82	239 ± 81	256 ± 90	237 ± 83†
LVESV (ml)	103 ± 52	101 ± 54	126 ± 73‡	104 ± 61*
LVEF (%)	58 ± 8	60 ± 8	54 ± 12‡	60 ± 9*
P/V ratio	1.5 ± 0.5	1.5 ± 0.6	1.9 ± 0.8‡	2.2 ± 1.1‡
RVEF (%)	46 ± 7	50 ± 8*	52 ± 12‡	59 ± 8*‡
RI	2.4 ± 0.6	2.0 ± 0.4*	1.8 ± 0.3‡	1.6 ± 0.2*‡

*$p < 0.01$, †$p < 0.05$, effects of nifedipine vs. corresponding control values (rest or exercise); ‡$p < 0.01$, effects of exercise vs. corresponding rest values (before or after nifedipine therapy). HR = heart rate; LVCO = total left ventricular output; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVSV = left ventricular stroke volume; MAP = mean arterial pressure; N = nifedipine; P/V ratio = pressure-volume ratio; RI = regurgitant index; RPP = rate-pressure product; RVCO = right ventricular forward cardiac output; RVEF = right ventricular ejection fraction; RVSV = right ventricular stroke volume; SVR = systemic vascular resistance.

Results

Patients without regurgitation. At rest, the mean regurgitant index was close to unity (1.04 ± 0.12, range 0.90 to 1.26) and was unchanged after nifedipine. The regurgitant index was not altered by exercise before (1.03 ± 0.07) and after (1.04 ± 0.08) nifedipine.

Aortic regurgitation (Table 1). *Rest.* After nifedipine, heart rate increased by 13% and mean arterial pressure decreased by 9% because of a lower systolic pressure as diastolic pressure was unchanged. The rate-pressure product overall was unchanged. There was no change in total left ventricular stroke volume; however, there was a 20% increase in forward stroke volume and a 36% increase in forward cardiac output associated with a significant decrease in regurgitant index. Systemic vascular resistance decreased by an average of 34% (Fig. 1). The change in systemic vascular resistance was related to the initial level of systemic vascular resistance (Fig. 2) and to the change in forward cardiac output and regurgitant index (Fig. 3). Mean left

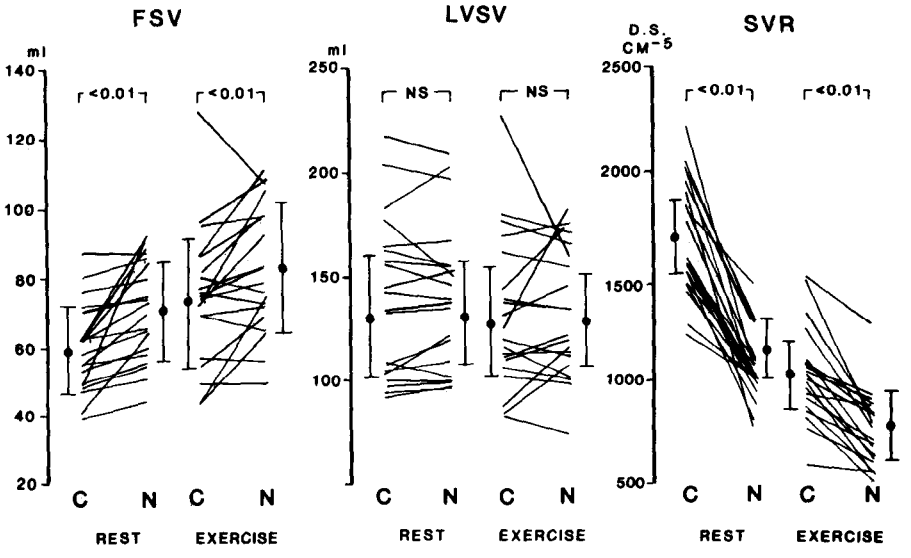

Figure 1. Right ventricular forward stroke volume (FSV), total left ventricular stroke volume (LVSV) and systemic vascular resistance (SVR) at rest and during exercise before (C) and after nifedipine (N) administration. D.S.CM-5 = dynes·s·cm^{-5}; NS = not significant.

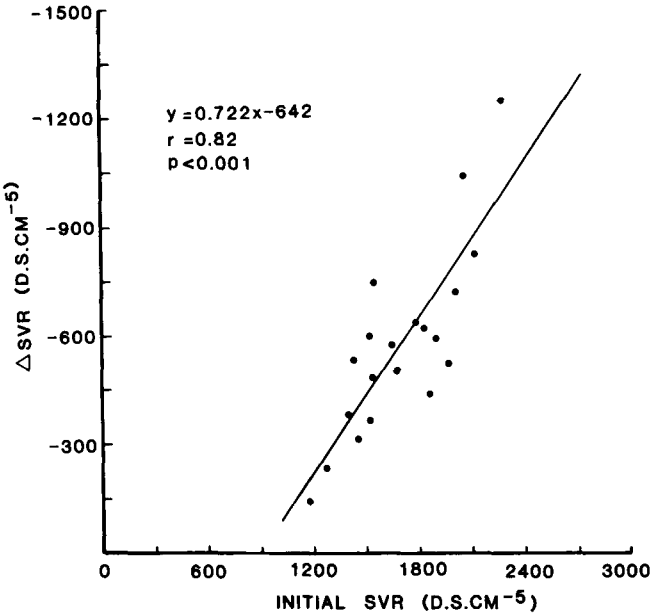

Figure 2. Relation between changes in systemic vascular resistance (ΔSVR) and initial systemic vascular resistance at rest. Patients with high baseline systemic vascular resistance at rest exhibited a large decrease in resistance after nifedipine administration. D.S.CM^{-5} = dynes·s·cm^{-5}.

ventricular end-diastolic and end-systolic volumes, ejection fraction and pressure-volume ratio did not change significantly (Fig. 4). Right ventricular ejection fraction increased.

Exercise. After nifedipine, at an identical level of exercise, heart rate increased by 9% and mean arterial pressure decreased by 8%, resulting in no change in rate-pressure product. Mean forward stroke volume was increased by 12%, but mean total left ventricular stroke volume was unchanged. As a consequence, total left ventricular output increased by 16% and forward cardiac output increased by 23%, associated with a further decrease in regurgitant index. Systemic vascular resistance decreased by an average of 19% (Fig. 1). Nifedipine tended to reduce systemic vascular resistance more when it was higher initially during control exercise ($r = 0.65$, $p < 0.01$).

Mean left ventricular end-diastolic volume was slightly but significantly decreased from 256 ± 90 to 237 ± 83 ml ($p < 0.05$). The major difference was in the mean end-systolic volume, which increased substantially during control exercise from 103 ± 52 ml at rest to 126 ± 73 ml during exercise ($p < 0.01$), but was unchanged after nifedipine administration from 101 ± 54 ml at rest to 104 ± 61 ml during exercise (p = NS). Thus, ejection fraction was higher than that during control exercise (Fig. 4). During nifedipine exercise, the decrease in left ventricular end-systolic volume was associated with a decrease in systolic blood pressure; consequently, the pressure-volume ratio was not significantly different. Right ventricular ejection fraction increased further.

Discussion

In this study, the average radionuclide regurgitant index for patients without valvular regurgitation was close to unity and was not changed by nifedipine or exercise. This agrees with the findings of other studies (20).

Hemodynamic effects of nifedipine in aortic regurgitation. In patients with chronic aortic regurgitation, nifedipine improved hemodynamics both at rest and during exercise. Left ventricular volumes decreased and ejection fraction improved, particularly during exercise. At rest, systemic vascular resistance decreased by a mean of 34% with nifedipine, which was greater than previously reported (8). This decrease appeared to be related to the initial level, with the higher levels showing the greatest decreases as has been reported previously (6,8,9). Forward stroke volume was increased significantly after nifedipine. The forward cardiac output increased and regurgitant flow decreased most in patients with an initially high baseline systemic vascular resistance. The rate-pressure product did not change in our study. In contrast, Fioretti et al. (8) found a 14% reduction in rate-pressure product due to a larger decrease in systolic blood pressure with the same dose of nifedipine. Their study was invasive and the vasodilator effect of angiographic con-

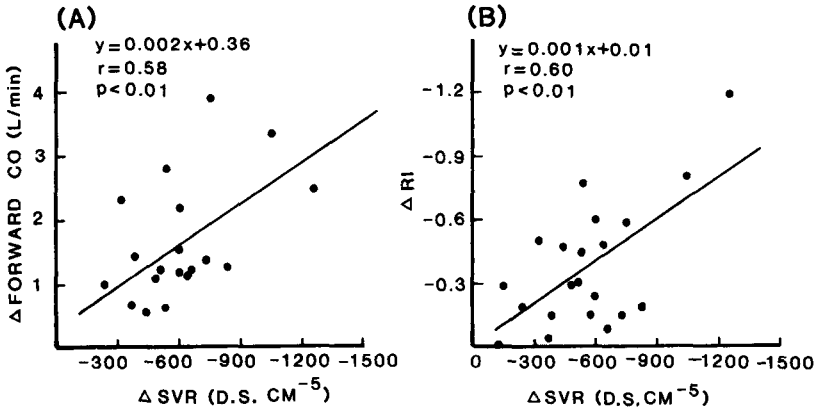

Figure 3. Relation between changes in systemic vascular resistance (ΔSVR) and changes in (**A**) forward cardiac output (ΔFORWARD CO) and (**B**) regurgitant index (ΔRI) after administration of nifedipine at rest. Note that patients with a large change in systemic vascular resistance had the greatest increase in forward cardiac output and greatest decrease in regurgitant flow. D.S.CM^{-5} = dynes·s·cm^{-5}.

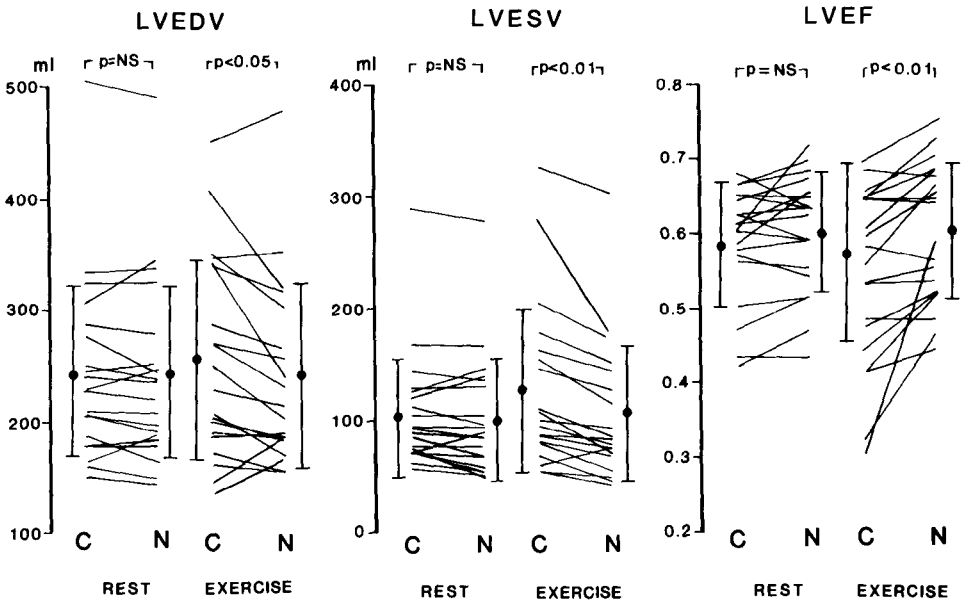

Figure 4. Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and left ventricular ejection fraction (LVEF) at rest and during exercise before (C) and after nifedipine (N) administration.

trast agent may have predisposed their patients to a greater hypotensive effect of nifedipine.

After nifedipine, left ventricular stroke volume and ejection fraction at rest remained unchanged, consistent with the previous findings (8,9) that after nifedipine a similar left ventricular performance is delivered at lower loading conditions.

Improved ventricular performance and reduced regurgitation after nifedipine. Although the response to nifedipine in patients with aortic regurgitation has been studied at rest (8,9), the changes during exercise are more important in determining overall responses to the drug in ambulant patients. The hemodynamic response to exercise in our patients before the administration of nifedipine confirmed previous findings (21,22) showing that although mean arterial pressure increased, forward stroke volume and cardiac output also increased and regurgitant flow decreased in association with an increase in heart rate and a reduction in systemic vascular resistance.

In the present study, the average left ventricular end-systolic volume significantly increased and left ventricular ejection fraction decreased during exercise, suggesting that the reduction in systemic vascular resistance induced by exercise alone did not adequately compensate for the increased hemodynamic burden on the left ventricle. The administration of nifedipine produced a further decrease in systemic vascular resistance in addition to that from vasodilation of exercise. This was associated with a faster heart rate, a lower mean arterial pressure and an increase in forward stroke volume and cardiac output. Although left ventricular end-diastolic volume was slightly decreased, nifedipine prevented the increase in end-systolic volume seen during control exercise, resulting in a higher left ventricular ejection fraction, and indicated an improvement in left ventricular performance. The pressure-volume ratio was not significantly changed, suggesting that these effects were due to changes in loading conditions. During exercise after nifedipine, the regurgitant flow was further decreased because of lower systemic vascular resistance and a faster heart rate.

Clinical implications. Acute afterload reduction with nifedipine improved hemodynamic status and cardiac performance and reduced regurgitant flow at rest and during exercise. The results of this short-term study suggest that the effects of long-term afterload reduction with nifedipine in patients with chronic aortic regurgitation should be investigated.

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